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EXAMINER
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/877,160	CHING-HSAING ET AL
	Examiner	Art Unit
	"Neon" Phuong Huynh	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/14/02; 1/13/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,19,20 and 29-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,19,20 and 29-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8*
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

1. Claims 16, 19-20 and 29-43 are pending.

2. Applicant's election with traverse of Group II, Claims 16-20 (now claims 16, 19-20 and 29-43) drawn to a method of treatment using milk comprising the allergen Der p5, filed 1/13/03, is acknowledged. The traversal is on the grounds that (1) the inventions are connected in design or operation since a milk composition is used in each case and Groups VII, VIII and IX are not independent since they are not unconnected in effect. (2) Upon allowance of generic claims, all claims drawn to species be allowed. This is not found persuasive because of the reasons set forth in the restriction mailed 11/7/02. Groups VII, VIII and IX are drawn to a method of treatment using milk comprising the distinct allergen such as Der p1, Der p2 and Der p5 that differ with respect to their amino acid sequences, structure and different effects. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group II (now claims 16, 19-20 and 29-43) and Groups I, III-XV is still deemed proper and is therefore made FINAL.

3. Claims 16, 19-20 and 29-43, drawn to a method of treatment using milk comprising the allergen Der p5, are being acted upon in this Office Action.

4. The references cited on PTO 1449 filed 1/14/02 have been crossed out because none of the cited references have been submitted to the Office.

5. Claim 19 is objected to because it drawn to Der p1 and Der p2, which are none-elected inventions.

6. The disclosure is objected to because of the following informality: incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 5, line 3 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-

executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database. Appropriate action is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 16, 19-20 and 29-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of suppressing airway inflammation and hyperactivity in the subject comprising oral feeding of a milk composition comprising a Dermatophagoides pteronyssinus allergen wherein said allergen is Der p5 of SEQ ID NO: 3, (2) the said method wherein the milk is obtained from a transgenic animal, **does not** reasonably provide enablement for (1) a method of treatment comprising administering *any* milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "heterologous, non-milk allergen" and a casein; (2) a method of treatment comprising administering any milk composition to any subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "Dermatophagoides pteronyssinus allergen", *any* "Der p5", *any* "Der p1", or *any* "Der p2"; (3) a method of decreasing the production of IgE in a subject exposed to any allergen, the method comprising administering to a subject *any* milk composition comprising *any* "heterologous, non-milk allergen", wherein the allergen is present in a sufficient quantity to induce in the subject tolerance to *any* allergen, the tolerance including suppression of allergen-specific IgE production in the subject upon subsequent exposure to *any* allergen; (4) The method of treatment comprising administering a milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "heterologous, non-milk allergen" and a casein wherein the allergen is *any* allergen of *any* insect, *any* allergen of dust mite, *any* allergen of dust mite Dermatophagoides pteronyssinus, or *any* allergen of dust mite Dermatophagoides farinae; (5) the method of treatment comprising administering a milk composition to a subject in a sufficient

amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "heterologous, non-milk allergen" and a casein wherein the milk is administered orally; (6) the method of treatment comprising administering a milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* Dermatophagoides pteronyssinus allergen, *any* Der p5, any Der p1, or any Der p2 wherein the milk is administered orally and (7) the method of decreasing the production of IgE in a subject exposed to *any* allergen, the method comprising administering to a subject *any* milk composition comprising *any* "heterologous, non-milk allergen", wherein the allergen is present in a sufficient quantity to induce in the subject tolerance to *any* allergen, the tolerance including suppression of allergen-specific IgE production in the subject upon subsequent exposure to any allergen wherein the milk is administered orally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three specific Der p 1, Der p2 and Der p5 from house dust mite Dermatophagoides pteronyssinus comprising SEQ ID NO: 1-3, respectively. The specification further discloses that only the Der p5 allergen is expressed in the milk of transgenic mice using the obvine alpha-lactabumin promoter. The mice that are fed with the transgenic milk containing the dust mite allergen Der p5 for 28 days have a reduction in the development of Der p5-induced specific airway inflammation as compared with mice treated with milk only.

The specification does not teach how to make and use *any* "heterologous, non-milk allergen", *any* "Dermatophagoides pteronyssinus allergen", *any* "Der p5", *any* "Der p1", or *any* "Der p2", *any* allergen of *any* insect, *any* allergen of dust mite, *any* allergen of dust mite Dermatophagoides pteronyssinus, or *any* allergen of dust mite Dermatophagoides farinae for a method of reducing airway inflammation and hyperactivity, or decreasing the production of IgE

by administering any milk composition comprising any undisclosed allergen mentioned above because there is insufficient guidance as to the structure such as the amino acid sequence of any allergen mentioned above without SEQ ID NO.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Further, the specification discloses only one specific allergen, that is Der p5 of SEQ ID NO: 3 from Dermatophagoides pteronyssinus produced by transgenic milk for the claimed method of reducing airway inflammation and hyperactivity, and decreasing the production of IgE exposed to said specific allergen. Given the indefinite number of undisclosed allergen, there is insufficient working, demonstrating that oral feeding of Der p5 in a milk composition would be efficacious for reducing airway inflammation and hypersensitivity to other undisclosed "heterologous non-milk allergen", much less any allergen from any insect, any dust mite such as *Dermatophagoides pteronyssinu,* or Dermatophagoides farinae.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Fasler *et al* teach that peptides derived from house dust mite Der p1 are modified by even a single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al*. further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Given the lack of guidance as to the structure of any protein such as any non-milk allergen mentioned above, a person of skill in the art would not know which undisclosed non-milk allergen is essential and could be used in the claimed therapeutic methods, much less using

the nucleic acid encoding said undisclosed allergen to express said protein in the milk of any transgenic animal, in turn, for a method of reducing airway inflammation and hyperactivity.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 16, 19-20 and 29-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of treatment comprising administering *any* milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "heterologous, non-milk allergen" and a casein; (2) a method of treatment comprising administering any milk composition to any subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "Dermatophagoides pteronyssinus allergen", *any* "Der p5", *any* "Der p1", or *any* "Der p2"; (3) a method of decreasing the production of IgE in a subject exposed to any allergen, the method comprising administering to a subject *any* milk composition comprising *any* "heterologous, non-milk allergen", wherein the allergen is present in a sufficient quantity to induce in the subject tolerance to *any* allergen, the tolerance including suppression of allergen-specific IgE production in the subject upon subsequent exposure to *any* allergen; (4) The method of treatment comprising administering a milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "heterologous, non-milk allergen" and a casein wherein the allergen is *any* allergen of *any* insect, *any* allergen of dust mite, *any* allergen of dust mite Dermatophagoides pteronyssinus, or *any*

allergen of dust mite Dermatophagoides fainae; (5) the method of treatment comprising administering a milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* "heterologous, non-milk allergen" and a casein wherein the milk is administered orally; (6) the method of treatment comprising administering a milk composition to a subject in a sufficient amount to reduce airway inflammation and hyperactivity in the subject, wherein the milk composition comprises *any* Dermatophagoides pteronyssinus allergen, *any* Der p5, any Der p1, or any Der p2 wherein the milk is administered orally and (7) the method of decreasing the production of IgE in a subject exposed to *any* allergen, the method comprising administering to a subject *any* milk composition comprising *any* "heterologous, non-milk allergen", wherein the allergen is present in a sufficient quantity to induce in the subject tolerance to *any* allergen, the tolerance including suppression of allergen-specific IgE production in the subject upon subsequent exposure to any allergen wherein the milk is administered orally.

The specification discloses only three specific Der p 1, Der p2 and Der p5 from house dust mite Dermatophagoides pteronyssinus comprising SEQ ID NO: 1-3, respectively. The specification further discloses that only the Der p5 allergen is expressed in the milk of transgenic mice using the obvine alpha-lactabumin promoter. The mice that are fed with transgenic milk containing the dust mite allergen Der p5 for 28 days have a reduction in the development of Der p5-induced specific airway inflammation as compared with mice treated with milk only.

With the exception of the specific allergen for the specific method of treatment to reduce airway inflammation and hyperactivity in the subject, there is insufficient written description about the structure associated with function of *any* "heterologous, non-milk allergen", *any* "Dermatophagoides pteronyssinus allergen", *any* "Der p5", *any* "Der p1", or *any* "Der p2", *any* allergen of *any* insect, *any* allergen of dust mite, *any* allergen of dust mite Dermatophagoides pteronyssinus, or *any* allergen of dust mite Dermatophagoides fainae without the amino acid sequence or SEQ ID NO. Sine the amino acid sequence of any allergen, the corresponding nucleotide sequence mentioned above is not adequately described, it follows that the method wherein the milk is obtained from a transgenic mammal is not adequately described.

Given the specification discloses only three specific Der p 1, Der p2 and Der p5 SEQ ID NO: 1-3, respectively, from only house dust mite Dermatophagoides pteronyssinus for a method of treatment of dust mite allergen comprising administering a milk composition comprising said allergen, one of skill in the art would reasonably conclude that the disclosure fails to provide a

representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 16, 20, 29-30, 34, and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,951,984 (Sept 1999; PTO 892).

The '984 patent teaches a method to induce tolerance in the subject by administering orally a milk composition comprising various non-milk allergen such as the white of the eggs, soybean protein, pollen, house dust mite, and tick (See column 7, lines 55-58, and lines 7-10, column 9, lines 65-66, claims 1-4 of '984 patent, in particular). The term "comprising" is open-ended. It expands the composition in the claimed method to include additional compound such as soybean oil to read on the reference treatment composition. The '984 patent further teaches in case when mother's milk, which inherently contains casein, is not available, commercial milk preparations for allergic disease may be used (see column 7, lines 56-58, in particular). The reference method inherently reduces airway inflammation and hyperactivity as well as reducing the reference allergens specific IgE production. Claim 29 is included in this rejection because dust mite is an allergen from insect. Thus, the reference teachings anticipate the claimed invention.

12. Claims 16, 20, 29-30, 34, and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,814,345 (Sept 1998, PTO 892).

The '345 patent teaches a method of treating allergic individual with a milk composition (oral vaccine) comprising a heterologous non-milk allergen such as dust mite to induce tolerance to said allergen (See entire document, column 8, lines 14-23, column 10, Table, in particular). The reference milk composition inherently contains casein which is a protein commonly found in

milk. The reference method inherently reduces airway inflammation and hyperactivity as well as reducing the reference allergens specific IgE production because the '345 patent teaches that oral consumption of milk obtained from immunized animal with any one specific allergen or a mixture of allergens desensitize the subject who ingested the milk composition; the subject acquire tolerance to such allergen (See column 5, lines 19-29, column 5, lines 66-67, in particular). The '345 patent teaches that the advantages of oral desensitization are that it can be self administered, less painful and less expensive than vaccines which must be injected (See column 5, lines 24-26, in particular). Claim 29 is included in this rejection because dust mite is an allergen from insect. Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 16, 19-20, 29-32, and 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,951,984 (Sept 1999, PTO 892) or US Pat No 5,814,345 (Sept 1998, PTO 892) each in view of Sato *et al* (Immunology 95(2): 193-9, Oct 1998; PTO 892), or Lin *et al* (J Allergy Clin Immunol 94: 989-96, 1994; PTO 892) or US Pat No 6,413,738 (July 2002, PTO 892).

The teachings of the '984 patent and the '345 patent have been discussed supra.

The claimed invention as recited in claim 19 differs from the teachings of the references only that the method wherein the milk composition comprising the allergen Der p5.

The claimed invention as recited in claims 31 and 40 differs from the teachings of the references only that the method wherein the dust mite is *Dermatophagoides pteronyssinus*.

The claimed invention as recited in claim 32 and 41 differs from the teachings of the references only that the method wherein the dust mite is *Dermatophagoides farinae*.

The claimed invention as recited in claims 42-43 differs from the teachings of the references only that the method wherein the allergen is Der p5.

Sato *et al* teach a method of treating airway inflammation and hyperactivity and decrease the allergen specific IgE production to a subject such as mice by administering orally a composition comprising a non-milk allergen such as dust mite extract from *Dermatophagoides pternyssinus* (Dp) to induce oral tolerance that suppresses allergen-specific IgE production in the subject such as sensitized mice upon subsequent exposure to the allergen (See abstract, in particular). The reference allergen is from dust mite, which is of an insect. Sato *et al* teach that oral feeding of allergen can induce oral tolerance that can modulate the production of allergen-specific IgE antibodies in both naïve and sensitized animals (See abstract, Discussion, in particular).

Lin *et al* teach dust mite allergen from *Dermatophagoides pternyssinus* Der p5 which is identical to the claimed SEQ ID NO: 1 (See Fig 2, in particular).

The '738 patent teaches oral administration of dust mite allergen such as Der f VII from *Dermatophagoides farinae* and/or Der p VII from *Dermatophagoides pternyssinus* can desensitize the subject to the allergic response to the reference dust mite allergens (See column 17, lines 42-56, column 18, line 7, column 19, lines 14-17, in particular). The '738 patent teaches high doses of allergen generally produce the best results during immunotherapy such as best symptom relief (See column 20, line 44-46, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the allergen such as egg protein, soybean protein, pollen or tick as taught by the '984 patent or the mite allergen as taught by the '345 patent for the *Dermatophagoides pternyssinus* allergen extract as taught by Sato *et al* or the Der p 5 allergen from dust mite of *Dermatophagoides pternyssinus* as taught by Lin et al or the Der f VII from dust mite of *Dermatophagoides farinae* as taught by the '738 patent for a method of treating comprising administering a milk composition comprising an allergen to reduce airway inflammation or to decrease the production of IgE as taught by the '984 patent, the '345 patent and the Sato et al. From the combined teachings of the references, it is apparent that one of

ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Sato *et al* teach that oral tolerance can improve its use allergy immunotherapy. Sato *et al* teach that oral feeding of allergen can induce oral tolerance that can modulate the production of allergen-specific IgE antibodies in both naïve and sensitized animals (See abstract, Discussion, in particular). Lin *et al* teach that Der p5 is another one of dust mite allergens from *Dermatophagoides pternyssimus* Der p5 (See Fig 2, in particular). The '738 patent teaches that oral administration of dust mite allergen such as Der f VII from *Dermatophagoides farinae* and/or Der p VII from *Dermatophagoides pternyssimus* can desensitize the subject to the allergic response to the reference dust mite allergens (See column 17, lines 42-56, column 18, line 7, column 19, lines 14-17, in particular). The '345 patent teaches that the advantages of oral desensitization are it can be self administered, less painful and less expensive than vaccines which must be injected (See column 5, lines 24-26, in particular).

16. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,951,984 (Sept 1999, PTO 892) or US Pat No 5,814,345 (Sept 1998, PTO 892) each in view of Sato *et al* (Immunology 95(2): 193-9, Oct 1998; PTO 892), or Lin *et al* (J Allergy Clin Immunol 94: 989-96, 1994; PTO 892) or US Pat No 6,413,738 (July 2002, PTO 892) as applied to claims 16, 19-20, 29-32, and 38-43 mentioned above and further in view of Wall *et al* (Proc Natl. Sci USA 88: 1696-1700, 1991; PTO 892).

The combined teachings of the '984 patent, the '345 patent, Sato et al, Lin et al and the '738 patent have been discussed supra.

The claimed invention as recited in claim 33 differs from the teachings of the references only that the method wherein the milk is obtained from a transgenic mammal.

Wall *et al* teach that a method of producing any pharmacologically active protein of interest in the mammary glands of transgenic mammal such as swine (pig) and it is possible to produce high levels of foreign protein milk of farm animals (See abstract, in particular). Wall *et al* teach that large quantities of milk would be easily obtained from dairy animals, however, the pig can carry 5 times as many fetuses as a cow, doe or ewe which requires one-sixth the number of animals used for obtaining a transgenic pig and less than half of the time in terms of recovery of injectable ova per donor gilt (See page 1696, column 2, first paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce transgenic milk comprising any allergen such as dust mite allergen from *Dermatophagoides pternyssinus* as taught by the '984 patent or the dust mite as taught by the '345 patent or the Der p5 allergen as taught by Lin *et al* or the allergen from *Dermatophagoides farinae* as taught by the '738 patent obtained from a transgenic mammal as taught by Wall *et al* for a method of treatment comprising administering a milk composition comprises any allergen from transgenic animal to reduce airway inflammation and hyperactivity in the subject as taught by the '984 patent, the '345 patent, Sato et al, Lin et al and the '738 patent and Wall et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Wall *et al* teach large quantities of milk would be easily obtained from dairy animals, however, the pig can carry 5 times as many fetuses as a cow, doe or ewe which requires one-sixth the number of animals used for obtaining a transgenic pig and less than half of the time in terms of recovery of injectable ova per donor gilt (See page 1696, column 2, first paragraph, in particular).

17. Claims 16, 19-20, 29-32, and 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato *et al* (Immunology 95(2): 193-9, Oct 1998; PTO 892) in view of US Pat No. 6,132,712 (Oct 2000, PTO 892) and Lin *et al* (J Allergy Clin Immunol 94: 989-96, 1994; PTO 892) or US Pat No 6,413,738 (July 2002, PTO 892).

Sato *et al* teach a method of treating airway inflammation and hyperactivity and decrease the allergen specific IgE production to a subject such as mice by administering orally a composition comprising a non-milk allergen such as dust mite extract from *Dermatophagoides pternyssinus* (Dp) to induce oral tolerance that includes the suppression of allergen-specific IgE production in the subject such as sensitized mice upon subsequent exposure to the allergen (See abstract, in particular). The reference allergen is from dust mite, which is of an insect. Sato *et al* teach that oral tolerance can improve its use allergy immunotherapy because the oral tolerance was able to modulate the production of allergen-specific IgE antibodies in both naïve and sensitized animals (See abstract, Discussion, in particular).

The claimed invention as recited in claim 16 differs from the reference only that the method wherein the composition is a milk composition comprising a casein

The claimed invention as recited in claim 19 differs from the teachings of the references only that the method wherein the milk composition comprising the allergen Der p5.

The claimed invention as recited in claims 31 and 40 differs from the teachings of the references only that the method wherein the dust mite is *Dermatophagoides pteronyssinus*.

The claimed invention as recited in claim 32 and 41 differs from the teachings of the references only that the method wherein the dust mite is *Dermatophagoides farinae*.

The claimed invention as recited in claims 42-43 differs from the teachings of the references only that the method wherein the allergen is Der p5.

The '712 patent teaches casein is a protein commonly found in milk and is useful for stabilizing any protein to survive proteolytic degradation via oral administration to permit absorption of any drug into the circulatory system (See column 3, lines 11-21, in particular).

Lin *et al* teach dust mite allergen from *Dermatophagoides pternyssinus* Der p5 which is identical to the claimed SEQ ID NO: 1 (See Fig 2, in particular).

The '738 patent teaches oral administration of dust mite allergen such as Der f VII from *Dermatophagoides farinae* and/or Der p VII from *Dermatophagoides pternyssinus* can desensitize the subject to the allergic response to the reference dust mite allergens (See column 17, lines 42-56, column 18, line 7, column 19, lines 14-17, in particular). The '738 patent teaches that high doses of allergen generally produce the best results during immunotherapy such as best symptom relief (See column 20, line 44-46, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include casein as taught by the '712 patent in a milk composition comprising any allergen such as dust mite from *Dermatophagoides pternyssinus* (Dp) as taught by Sato et al or *Dermatophagoides pternyssinus* Der p5 as taught by Lin et al or the Der f VII from *Dermatophagoides farinae* as taught by the '738 patent for a method of to reduce airway inflammation and hyperactivity and to decrease the allergen specific IgE as taught by Sato et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '712 patent teaches casein is a protein commonly found in milk and is useful for stabilizing any protein to survive proteolytic degradation via oral administration to permit absorption of any drug into the circulatory system (See column 3, lines 11-21, in particular). Sato *et al* teach that oral tolerance can improve its use allergy immunotherapy Sato *et al* teach that oral feeding of allergen

can induce oral tolerance that can modulate the production of allergen-specific IgE antibodies in both naive and sensitized animals (See abstract, Discussion, in particular). The '738 patent teaches oral administration of dust mite allergen such as Der f VII from *Dermatophagoides farinae* and/or Der p VII from *Dermatophagoides pternyssinus* can desensitize the subject to the allergic response to the reference dust mite allergens (See column 17, lines 42-56, column 18, line 7, column 19, lines 14-17, in particular).

18. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sato *et al* (Immunology 95(2): 193-9, Oct 1998; PTO 892) in view of US Pat No. 6,132,712 (Oct 2000, PTO 892) and Lin *et al* (J Allergy Clin Immunol 94: 989-96, 1994; PTO 892) or US Pat No 6,413,738 (July 2002, PTO 892) as applied to claims 16, 19-20, 29-32, and 38-43 mentioned above and further in view of Wall *et al* (Proc Natl. Sci USA 88: 1696-1700, 1991; PTO 892).

The combined teachings of Sato *et al*, the '712 patent, Lin *et al*, and the '738 patent have been discussed supra.

The claimed invention as recited in claim 33 differs from the reference only that the method wherein the milk is obtained from a transgenic mammal.

Wall *et al* teach that a method of producing any pharmacologically active protein of interest in the mammary glands of transgenic mammal such as swine (pig) and it is possible to produce high levels of foreign protein milk of farm animals (See abstract, in particular). Wall *et al* teach that large quantities of milk would be easily obtained from dairy animals, however, the pig can carry 5 times as many fetuses as a cow, doe or ewe which requires one-sixth the number of animals used for obtaining a transgenic pig and less than half of the time in terms of recovery of injectable ova per donor gilt (See page 1696, column 2, first paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce transgenic milk comprising any allergen such as dust mite allergen from *Dermatophagoides pternyssinus* as taught by Sato et al or the Der p5 allergen as taught by Lin *et al* or the Der pf VII allergen from *Dermatophagoides farinae* as taught by the '738 patent in the milk obtained from a transgenic mammal as taught by Wall *et al* containing casein as taught by the '712 patent for a method of to reduce airway inflammation and hyperactivity in the subject as taught by the Sato *et al*, the '712 patent, Lin *et al*, the '738 patent and Wall *et al*. From the combined teachings of the references, it is apparent that one of ordinary

skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Wall *et al* teach large quantities of milk would be easily obtained from dairy animals, however, the pig can carry 5 times as many fetuses as a cow, doe or ewe which requires one-sixth the number of animals used for obtaining a transgenic pig and less than half of the time in terms of recovery of injectable ova per donor gilt (See page 1696, column 2, first paragraph, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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